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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94304-1050

EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 11/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/003,462	SIERRA ET AL.	
	Examiner	Art Unit	
	Anne L. Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/5/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-19* is/are pending in the application.

4a) Of the above claim(s) *14-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' amendment filed 9/05/2006 is acknowledged.

2. Claim 3 was canceled. Claim 19 was added. Claims 1, 2, and 4-18 are pending. Claims 14-19, drawn to non-elected inventions, are withdrawn from consideration. Claims 1, and 4-13 are examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

4. The rejection of claims 1 and 2 under 35 U.S.C. 102(b) as being anticipated by either Heimbrook (Heimbrook, D.C. et al., Proc. Natl. Acad. Sci., USA, 87: 4697-4701, 1990) or Kunwar (Kunwar, S. et al., J. Neurosurg., 79: 569-576, 1993) as evidenced by Chaudhary (Chaudhary, V.K. et al. Proc. Natl. Acad. Sci., USA, 84, pp4538-4542, 1987) is withdrawn in view of the amendment limiting the carrier protein to P64k.

5. The objection to claims 1, 2, 4, 5, and 7-11 because of the use of the term TGFα instead of human TGFα or hTGFα is withdrawn in view of the amendment.

6. The objection to the specification for not being in compliance with the sequence rules is withdrawn in view of the preliminary amendment filed Nov. 6, 2002. This application is now in compliance with the sequence rules.

7. The rejection of claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Hoeprich (Hoeprich, Jr., P.D. et al., The Journal of Biological Chemistry, 254(32): 19086-19091, 1989) is withdrawn in view of the amendment limiting the carrier protein to P64k. However, a rejection under 103(a) is made. See below.

Claim Rejections Maintained:

8. Claims 8, 9, 10 and 11 are/remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for vaccines comprising an EGF molecule sufficiently characterized by physical or chemical structure, such as by SEQ ID NO, does not reasonably provide enablement for vaccines comprising EGF molecules identified solely as "EGF". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants' arguments have been carefully considered but fail to persuade. Applicants appear to misconstrue the basis for this rejection. The rejection is made because the specification provides a definition of the term "EGF" that includes fragments, and variants. The specification defines the scope of the term "EGF" as including any fragment derived from EGF that has the same immunology properties and/or similar effects to the original molecule; the specification further includes original substitutions of amino acids, change of specific amino acids that

increase the stability and/or activity, chemical modifications, and other changes to structure (page 7, paragraph 42). Because the definition of "EGF" includes molecules having very little structural similarity, one of skill in the art would have to practice further and undue experimentation to know how to use the claimed inventions. Applicants point out that the term "EGF" may be used as a search term in databases such as GenBank, and that thousands of submissions may be found. Applicants use that as a basis for asserting that the structure of EGF is known and well documented. The examiner is not questioning how one of skill in the art would know how to use full-length EGF, but instead is questioning how one may know how to use the claimed inventions having the scope that is implied by the definition provided by the specification. The definition provided by the specification allows a broad interpretation of the claims, because the definition provides no structure and is loosely defined as compounds that have "the same immunology properties and/or similar effects to the original molecule". What is included in "immunology properties"? Just the ability to be haptenized so that antibodies may be formed? Such a property applies to almost any protein. What is included in "other changes to structure"? Therefore, the rejection is maintained for the reasons of record.

9. Claims 8, 9, 10 and 11 are/remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the specification fails to provide an

adequate description of "EGF". This rejection is based on the interpretation of the terms "EGF" encompassing a genus of molecules that are not adequately described by the specification.

Applicants' arguments have been carefully considered, but fail to persuade. The examiner acknowledges that EGF is a well-known compound, the structure of which is in the prior art. However, the basis for this rejection is that the genus of compounds encompassed by the claims is broader than what is exemplified in the specification, which is the use of full-length human EGF. The definition provided by the specification allows a broad interpretation of the claims, because the definition provides no structure and is loosely defined as compounds that have "the same immunology properties and/or similar effects to the original molecule". Because of the scope of the term and the lack of correlation between structure and function, the working examples provided in the specification are not sufficient to provide support for the broadly claimed inventions.

Double Patenting

10. The provisional rejection of claims 1, 2 and 4-13 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7, 10, 11, 12, 23, and 26 of copending Application No. 10/005,341 is maintained for the reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of copending application 10/005,341 appear to claim compositions that fall within the scope of the vaccine compositions comprising conjugates or fusion proteins of TGFα and a carrier protein.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants' remarks concerning holding this rejection in abeyance until allowable subject matter is identified is acknowledged.

New Grounds of Rejection:

11. Claims 1, 2, and 4-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it contains a reference to "any carrier protein" and then "said protein". This rejection would be overcome by amending claim 1 to recite "a carrier protein" instead of "any carrier protein".

Claims 10 and 11 are indefinite because they are both drawn to compositions comprising a mix of two vaccine preparations. However, when the components of the mixture are set forth in the claim, the word "or" is used instead of "and". This rejection would be overcome by amending claim 10 to read "...comprising a mix of two vaccine preparations, one preparation containing P64k coupled by a chemical method to hTGFα, and the other preparation containing P64k coupled by a chemical method to EGF ...", and claim 11 to read "...comprising a mix of two vaccine preparations, one preparation containing a fusion protein between P64k and hTGFα, and the other preparation containing a fusion protein between P64k and EGF ...".

Claims 4, 5 and 6 are indefinite because of the recitation off the term "gene". As the claims are currently drawn, it appears that these claims are drawn to vaccine compositions comprising fusion proteins produced by recombinant technology, where a nucleic acid (not a "gene", which is a term used to indicate a nucleic acid found in nature) that encodes the fusion protein is cloned into an expression vector system and expressed in mammalian cells, bacteria or yeast. Lewin (Lewin, B., Genes V, Oxford University Press, Oxford, 1994, page 1242) defines "gene" as including regions preceding and following the coding region as well as intervening sequences between individual coding segments.

12. Claims 1, 2 and 4-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising human TGFα linked to P64k either by chemical means or as a fusion protein, where the intended use is that of inducing an immune response to human TGFα, the specification does not reasonably provide enablement for vaccines comprising human TGFα linked to P64k either by chemical means or as a fusion protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The basis for this rejection is that the specification fails to enable one of skill in the art to use the claimed compositions as prophylactic cancer vaccines for the intended use of preventing cancer.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence

or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The claims are drawn to vaccine compositions. Because of the use of the term "vaccine", the claims read on compositions that have the intended use of cancer prevention. The specification provides no working embodiments demonstrating prevention of cancer using the claimed compositions. Therefore, the teachings of the specification are prophetic.

For methods that relate to the prevention of cancer, there is no guidance in the specification for determining the appropriate time prior to the development of tumors to begin the therapy or for identifying patients at risk for developing those tumors. Further, Chamberlain (Chamberlain, R.S. et al. Expert Opinion on Pharmacotherapy, 1(4): 603-614, 2000) teaches that while vaccines are classically administered prophylactically to evoke an immune response capable of providing protection against infection by the same or similar pathogens for the treatment of infectious diseases, this has not been the approach in the field of cancer immunotherapy. In the treatment of infectious diseases, there is an a priori inoculation with a pathogen resulting in protection on subsequent encounter. However, cancer is not an infectious process. Cancer cells express a limitless number of antigens and a priori knowledge of who in the population is at risk for which cancer is lacking (see page 604, 1st column, first full paragraph). The specification provides insufficient guidance in regard to the use of the claimed vaccines for the prevention of cancer, and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed compositions for use in the prevention of

cancer with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to use the claimed compositions as preventative vaccines.

Thus, in view of the contemporary knowledge in the art of the general lack of successful applications of vaccines for the prevention of human cancer as discussed above, as well as the lack of sufficient guidance in the specification, one of skill in the art would be forced into undue experimentation in order to use the invention as claimed. This rejection would be overcome if the claims are amended to be drawn to "compositions" instead of "vaccine compositions".

13. Claims 1, 7, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeprich (of record) in view of Gonzalez (Gonzalez, S. et al, Scandinavian J. Immunol., 52: 113, 2000, August).

Hoeprich teaches a conjugate of human TGFα and keyhole limpet hemocyanine, coupled using gluteraldehyde (see page 19087, 1st column). The TGFα was either chemically synthesized or recombinantly synthesized (see Figure 2 on page 19088 and page 19087, 1st column). The resulting conjugate was immunogenic (see Figure 2, and page 19088, 1st column). The adjuvant used was Freund's complete adjuvant (see page 19087, 2nd column), and also Freund's incomplete adjuvant (see 19087, 1st column). Hoeprich fails to teach a conjugate of human TGFα and P64k. However, Gonzalez teaches that P64k may be used as a substitute for various protein carriers. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have altered the conjugate taught by Hoeprich in view of the teachings of Gonzalez to make the claimed inventions. One would have

been motivated to make a conjugate with hTGFα with P64k because of the teachings of Gonzalez that P64k is a readily available immunological carrier, as efficient as other commonly used large carriers.

14. Claims 1, 4-6, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeprich (of record) in view of Gonzalez (Gonzalez, S. et al, Scandinavian J. Immunol., 52: 113, 2000, August) and further in view of Gonzalez-1997 (of record).

Within the scope of the claims is vaccine compositions comprising fusion proteins between hTGFα and P64k. The combination of Hoeprich and Gonzalez-2000 suggests a P64k carrier protein linked to hTGFα by gluteraldehyde linkage, but fails to suggest a recombinant fusion protein combining hTGFα and P64k. However, the use of recombinant fusion proteins comprising tumor associated antigens such as EGF, a ligand that binds EGFR, and P64k is known in the art as evidenced by Gonzalez-1997. Further, the use of adjuvants such as $Al(OH)_3$ is known in the art as evidenced by Gonzalez-1997. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a fusion protein linking hTGFα to P64k. Gonzalez-1997 teaches that a fusion protein has similar results to a chemically conjugated immunogen in the treatment of tumor bearing mice, but that a fusion protein has advantages in that production of the fusion protein may be scaled up reproducibly (see pages 97 and also 99). Therefore, one of ordinary skill in the art would have been motivated to make a fusion protein comprising hTGFα of Hoeprich linked to P64k as taught by Gonzalez-1997 to make the claimed inventions.

15. Claims 1, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeprich (of record) in view of Gonzalez (Gonzalez, S. et al, Scandinavian J. Immunol., 52: 113, 2000, August), in view of either Gonzalez-1997 (of record) or Gonzalez-1998(of record), and further in view of De Luca (De Luca, A. et al., Oncogene, 19(51): 5863-5871, 2000, Nov.).

Claim 1 includes within its scope a vaccine preparation that is a mixture of human TGFα and another EGFR ligand, where both human TGFα and the other EGFR ligand is linked to P64k carrier protein, either by recombinant technology or by a chemical linker. Claims 10 and 11 are drawn to vaccine compositions that are mixtures of human TGFα linked to P64k and EGF linked to P64k, where the linkage between the antigen and P64k is made either by recombinant methods to make fusion proteins (claim 11) or by chemical linker methods to make conjugates (claim 10). The combination of Hoeprich and Gonzalez-2000 suggests a composition comprising human TGFα linked to P64k. The combination of Hoeprich, Gonzalez-2000 and Gonzalez-1997 suggest a composition comprising a fusion protein of TGFα and P64k. Gonzalez-1997 explicitly teaches a composition comprising a fusion protein of EGF and P64k. Gonzalez-1998 explicitly teaches a composition comprising a conjugate of EGF linked to P64k. The combination of Hoeprich, Gonzalez-2000, Gonzalez-1997, Gonzalez-1998 fails to teach a vaccine composition that is a mixture of two vaccine preparations. However, epidermal growth factor receptor has multiple ligands and De Luca teaches that targeting more than one ligand is more effective than targeting a single ligand (see abstract). De Luca teaches the use of antisense technology to target EGFR ligands. However, De Luca is cited for the purpose of demonstrating that targeting more than one EGFR ligand is a strategy that is more efficacious than targeting only one ligand. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time

the invention was made to have used the combined teachings of Hoeprich, Gonzalez-2000, Gonzalez-1997 and Gonzalez-1998 to make a vaccine that comprised both an EGF vaccine and a TGFα vaccine, either in the form of a conjugate between EGFR ligand and P64k, or in the form of fusion proteins between EGFR ligand and P64k. One would have been motivated to make a combination vaccine preparation because of the teachings of De Luca demonstrating greater efficacy when more than one EGFR ligand is targeted.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
November 7, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER